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CLINICAL PROCEEDINGS

OF THE CHILDRENS HOSPITAL

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CONTENTS

IDIOPATHIC MEGACOLON. *John F. Gillespie, M.D., and Joseph J. McGovern, M.D.* 1

INFANTILE CORTICAL HYPEROSTOSIS. *Eulaine Naiden, M.D.* 6

REPORT OF TWELVE CASES OF ACUTE POLIOMYELITIS TREATED WITH BISTRIUM (C 6). *Stanley Wolf, M.D., and Frances J. Mastrota, M.D.* 9

CLINICO-PATHOLOGICAL CONFERENCE 10

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IDIOPATHIC MEGACOLON*

Special Report No. 221

John F. Gillespie, M.D.
Joseph J. McGovern, M.D.

The purpose of this paper is to advance a system of diagnosis and management of patients with idiopathic megacolon. The etiologic factors, pathology, complications, and physiologic basis for the use of drugs and various types of surgical procedures is presented and discussed.

During the past seventeen years (1934–1951), at The Children's Hospital, Washington, D. C. experiences in diagnosis and treatment of idiopathic megacolon have not been encouraging. In over 110,000 admissions, 40 cases have been diagnosed as idiopathic megacolon, of which 16 fulfilled roentgenographic criteria for the diagnosis. Of the remainder, 6 must be considered doubtful because of incomplete records and 18 were definitely not idiopathic megacolon, but included such conditions as imperforate anus, fecal impaction, presacral coccygeal tumor with constricting band about the rectum and redundant hypotonic colon. In this series, the incidence of the disease is about 1:7000 hospital admissions which is a slightly higher rate than that usually reported. The age range of these patients was from 3 weeks to 10½ years and there were 13 males and 3 females.

The treatment was subject to wide variation in the 16 proven cases. Six received only supportive therapy, while 6 received mecholyl and 2 each received syntropan and prostigmine. Of the remainder, 5 came to operation. Exploratory laparotomies were performed on 2; fecal impactions were broken in 2 cases, and 1 patient had a volvulus which was resected.

It is felt that a comprehensive review of the subject might lead to the establishment of more definite criteria for diagnosis and the development of a more standardized therapeutic regimen.

HISTORY AND DEFINITION

In 1888, Hirschsprung[1] published the first classical description of this condition and the term Hirschsprung's disease was coined. Idiopathic hypertrophy of the colon, pelvirectal achalasi, Mya's disease and idiopathic megacolon are synonyms. By definition, idiopathic megacolon is a rare disorder of unknown congenital etiology, which has resulted in hypertrophy and dilatation of the colon or portions of the colon and characterized by abdominal distension and obstipation.

* Abstract of an original article.

ETIOLOGY

Although the exact etiology remains in doubt, it is generally considered that the disease has a congenital origin and a developmental defect influences the function of the distal colon. A dysfunction of neuromuscular mechanism[2] with either hyperactivity of the sympathetic nervous system or hypoactivity of the parasympathetic nervous system is felt to be produced by this defect. In some cases of idiopathic megacolon, degenerative microscopic changes in the myenteric plexi (Auerbach's[3]), which are the lower motor neurons of the parasympathetic nervous system, have been reported. This lack of innervation could be responsible for the failure of passage of normal peristaltic waves across a given segment of alimentary canal. Such a situation, in effect, provides an obstruction which leads to dilation of the proximal segment of the colon.

PATHOLOGY

At operation, the intestinal wall is hypertrophied and feels like a wet leather glove.[4] The lumen is as much as ten to twenty times its normal size. The mucosa shows signs of chronic inflammatory changes, such as hypertrophy, fissures, ulcerations, perforations, and even what some writers term: ulcerative colitis. Microscopically, all layers are hypertrophied; the submucosa shows infiltration with round cells, ganglion cells and fibers of Auerbach's plexus are often vacuolated,[5] absent or imperfectly formed. The sigmoid alone is involved in 33 per cent of cases of idiopathic megacolon,[6, 7] sigmoid and rectum in 40 per cent and the cecum is involved in 40 per cent.

CLINICAL FEATURES

The incidence of idiopathic megacolon is reported to be 1 case in 9,000 to 10,000 hospital admissions. In our review of 110,000 admissions to The Children's Hospital, there were 16 cases, an incidence of 1:7,000. Males are affected four times as often as females, and the disease has been reported in five members of one family.[8]

The cardinal symptoms are obstinate constipation and abdominal distension, but some patients never have severe symptoms and their disease may be discovered accidentally during a diagnostic study for some other condition. Obstinate constipation develops slowly during the first three months of life and diarrhea may alternate with obstipation as bowel obstruction occurs. Abdominal pain is usually absent. Systemic symptoms, Bor-borygmus, dyspnea, paroxysmal tachycardia, and pre-cordial pain are not uncommon.[9]

On physical examination, the abdominal circumference may be greater than the height of the patient. The muscles of the abdominal wall are atrophied; the skin, thin and shiny; and peristaltic waves visible. Fecal

masses are often palpated and sigmoidoscopic examination reveals an enormously enlarged rectum and sigmoid. The introduction of air through the sigmoidoscope does not provoke constriction of the bowel lumen.

X-RAY

A flat plate of the abdomen, in the upright position, should precede barium studies. Fluoroscopic observation is essential during flow of barium to lend correct interpretation to the roentgenograms. A large amount of barium residue in post evacuation films is a good indication of disturbed colonic function. Swenson[10, 11] manipulated the bowel under fluoroscopy and demonstrated an area of spasm in the rectosigmoid in many cases.

The hazards of barium enema examination include potential impaction of retained masses of barium, and disagreeable cardio-respiratory symptoms, hence cleansing enemas should always follow this procedure.

In children, the diagnosis of idiopathic megacolon is suspected with a history of obstipation and marked abdominal distension, confirmed by barium enema and sigmoidoscopy, and verified when congenital or acquired defects of the rectum and anus and obstructive causes of megacolon have been ruled out. Of these last, a slow-growing scirrhous malignancy of the sigmoid must be considered. Also in the differential diagnosis are rickets, tuberculous peritonitis, cretinism, celiac disease, redundant hypotonic colon and behavior problems.

Formerly, the prognosis was not favorable because lives were claimed before the age of 5 years from inanition, debility, bronchopneumonia, myocardial failure, volvulus, and peritonitis from intestinal perforation. Mortality rate of untreated cases is over 80 per cent; those treated medically, 50 per cent[12]; and those treated surgically, 4.5 per cent.

Complications include volvulus, fecal impaction, intussusception, and perforation with peritonitis.[13, 14, 15]

TREATMENT

Since Hirschsprung's report on megacolon, the treatment of this condition has changed almost each decade and varied from simple conservative to radical and neurosurgical means. The proponents of the different types of therapy present case history proofs of cures with their particular form of treatment and this causes confusion. This dilemma undoubtedly results from the lack of knowledge of the etiology and until the etiology is definitely established, the confusion will exist. Possibly all cases of megacolon will not respond to one form of therapy, that is, the cases and types of treatment may have to be individualized.

There are five major forms of treatment. Each of these will be discussed briefly.

SUPPORTIVE THERAPY

When megacolon is suspected or diagnosed, the patients should be hospitalized for supportive therapy and evaluation. All efforts should be directed to improve the general health and to prevent it from becoming further deteriorated. These include:

1. *Diet*—Deletion of all foods which have a tendency toward constipation.
2. *Exercise*—Should be given regularly.
3. *Abdominal exercises*—are recommended to maintain tone in abdominal muscles.
4. *Regular bowel habits*—should be established.

DRUG THERAPY

Among the drugs used in former days were pancreatic extract,[16] parathormone,[17] arsenic, and iron. Recently, sympathetic and parasympathetic stimulants have come into prominence. A brief review of the pharmacology of the autonomic nervous system reveals that at the myoneural junction, parasympathetic impulses are activated by acetylcholine and sympathetic impulses by adrenalin. The action of the parasympathetic and sympathetic systems are opposing, so that the usual effect of parasympathetic stimulation is excitatory to the gastrointestinal tract and inhibitory to the sphincters, while the reverse effect is noted under sympathetic stimulation. The motility of the gastrointestinal tract depends, therefore, on the state of activity or underactivity of parasympathetic and sympathetic nervous systems.

Parasympathetic depressants have been used with good results. Atropine has some toxic side effects and is not generally used. Syntropan[18] does not have the toxic and drying effects of atropine. In some respects, the use of parasympathetic depressants is theoretically paradoxical, but one is forced to accept it on the basis that it is effective, the means by which it acts being, as yet, unexplained.

Parasympathetic stimulants have been in use since 1940.[19, 20] Acetylcholine is unstable in vivo but mecholyl produces a definite and continued stimulation of the parasympathetic nerves, usually without toxic manifestations. Numerous reports of beneficial results with this form of treatment have appeared.[21, 22, 23] Pilocarpine physostigmine and donyl have been used with some success.[24, 25]

Spinal anesthesia is considered by some authors[26, 27] as an effective empirical method of treatment for this disease since it often initiates normal bowel activity for long periods of time. Spinal anesthesia can be utilized as

a therapeutic test in prognosticating the value of sympathectomy in a given case. A comparison of pre- and post-anesthesia barium enema studies is useful in this regard.

Sympathectomy has been employed with much success to increase bowel activity since 1924.[28, 29] Again this is an empirical approach to the problem and presents the following disadvantages:

1. Sensation for visceral pain is destroyed and volvulus may occur without painful warning.
2. Sterility may follow in males.
3. Children under the age of four years tolerate this operation poorly.

Colonic resection. At the Lahey Clinic,[30] subtotal colectomy is considered the treatment of choice. The most recent advance by Swenson et al[10, 11] consists of abdominal-perineal resection of the rectum and recto-sigmoid which effectively eliminates the malformation causing rectosigmoid achalasia.

MANAGEMENT

Keeping in mind that a definite etiological factor has not been established for idiopathic megacolon, the authors feel that some plan of management is desirable even though the plan may be tentative and vulnerable to adverse criticism. Although it appears that no single form of treatment is applicable to all cases, there is now, with more variety of treatment, a greater chance of benefiting if not curing, every case.

With the presentation of a patient with the signs and symptoms suggestive of megacolon, efforts should be directed toward ruling out any possible organic obstruction in the lower gastro-intestinal tract and factors depressing the metabolic effectiveness of the smooth muscle of the colon. If these studies are negative and the sigmoidoscopic and barium enema examinations are positive, then a diagnosis of idiopathic megacolon may be made.

Once the diagnosis is established, the patient should be put on the aforementioned supportive treatment, and at the same time be given a trial of drug therapy for at least three months.

During this time, air balloon studies and roentgenological examinations may be made in an effort to demonstrate the existence of dysfunction or achalasia of the rectosigmoid. If there is no improvement under the conservative regime, and the latter examinations are positive, then the patient should be subjected to segmental resection of the involved area of achalasia.

If the studies are negative in establishing rectosigmoidal achalasia, and the medical treatment has failed; a trial of spinal anesthesia may be done and only if there is a profound response in the evacuation films, may sym-

pathecotomy be considered. If all the above studies, treatment, and examinations are negative, then the patient should be subjected to subtotal or total colectomy depending upon the extent of the colon involved.

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INFANTILE CORTICAL HYPEROSTOSIS

Case Report No. 222

Eulaine Naiden, M.D.

C. M., a four month old colored male, was admitted to the Children's Hospital on August 9, 1951 with the chief complaint of bilateral swelling of the jaws, fever and irritability. The onset of his illness had occurred three weeks earlier when his parents first noted irritability and fever which had persisted without other symptoms. Four days later, swelling developed below the right ear. A private physician was consulted and he suggested the diagnosis of tumor or mumps. Two injections of penicillin were given. The swelling subsided in a few days, but reappeared shortly thereafter. At this time treatment with terramycin was insitituted, but this was discontinued within five days because of diarrhea. In the meantime the opposite cheek became similarly involved and the child developed thrush. Because of increasing irritability, persistent fever, and continued bilateral swellings of the jaws, the child was brought to the hospital.

During his illness the child developed progressive anorexia, his food intake being about one-half of normal at the time of admission. He had lost an unknown amount of weight since the onset of illness. Except for a two-day bout of diarrhea, previously mentioned, the bowel movements had been normal. Vomiting had occurred twice.

There was no history of exposure to tuberculosis or to other known infectious diseases. Both parents and two infant siblings were well. The patient himself had had no other illnesses and since birth had been on an adequate evaporated milk formula. At one month of age he was started on 5 drops of oleum percomorphum daily. Solid foods were given at two months, but orange juice was refused by the patient.

Physical examination revealed a well nourished and developed, extremely irritable Negro male infant with bilateral swollen, firm areas with indistinct borders 2 inches in diameter, just anterior to the angles of the jaw and situated deeply within the tissues. There was no change in color or temperature of the area. A few shotty lymph nodes were palpable in the posterior cervical chains, and moderate pharyngeal hyperemia was present.

During his hospital stay, the patient's temperature fluctuated between 101.0 F. and 99.0 F. rectally. Urinalysis on admission revealed 2 to 3 erythrocytes and 3 to 5 leukocytes per high power field with many mucous shreds. Blood examination showed: hemoglobin, 11 grams; red blood cells, 4,100,000; white blood cells, 11,800 with 67 polymorphonuclear neutrophiles, 29 lymphocytes, and 4 monocytes per 100 cells.

Roentgenographic examination on the day following admission disclosed considerable soft-tissue swelling over the mandible with considerable subperiosteal hyperostosis of the mandibles. There was no evidence of abnormality of the long bones. The patient was discharged two days later with the diagnosis of infantile cortical hyperostosis or Caffey-Smyth syndrome.

DISCUSSION

The illness described above represents a classical picture of the syndrome first described by Caffey and Silverman[1] in 1945. The following year, Smyth, Potter and Silverman[2] reported and analyzed a series of cases, and the syndrome became definitely established and described as infantile cortical hyperostosis. Since then, the rapidly growing number of case reports reveals that the syndrome has a characteristic and rather readily recognizable pattern of symptoms and findings.

The illness occurs in previously healthy infants usually within the first four months of life (two cases have been reported at eighteen and twenty months). There is no sex predilection. The first symptom is irritability, usually associated with low-grade fever. Shortly thereafter, there develops a swelling of some part of the body. These swellings are firm, tender, and appear to be present in the deep tissues. Increased focal heat or reddening is not observed, nor are the swellings associated with fluctuation or adenopathy. In a few weeks, x-ray changes in the underlying bone and, occasionally, in apparently uninvolved areas are demonstrable. They are seen as deposits of subperiosteal new bone having a lamellated appearance. Any bone may be involved—the most common being the mandibles, clavicles, ribs, scapulae and long bones of the limbs.

The illness runs a protracted course and may be active for two to nine months, during which time the enlargement may subside and reappear in the same or different areas. Extreme irritability and fluctuating low-grade fever are common accompanying symptoms. Frequently, a mild hypochromic anemia and a mild leukocytosis is present. The sedimentation rate is elevated.

The disease is benign, all pathologic changes eventually clear completely. Bowing of the tibia may persist for some time, but eventually it, too, returns to normal.

The pathologic picture is that of an actively proliferating periosteum with simple hyperplasia of the underlying cortex. The lamellations seen on x-ray represent new layers of subperiosteal bone laid down with each exacerbation. The cortex becomes gradually absorbed from within and the medullary cavity widens. When the disease begins to subside, the process reverses. The cortex thins and the medullary cavity widens as bone is resorbed from within. Eventually, both cortex and medullary cavity decrease in size until the normal bone structure is restored.[3]

The etiology of the disease remains as obscure as does an effective method of treatment. It has been proposed that because of the fever, swelling, leukocytosis, and rash (which occasionally precedes the disease), an infection may be responsible. However, no response has been obtained from antibiotic therapy, and cultures of biopsy specimens have been sterile. Attempts to isolate a virus have thus far been unsuccessful.

Rothman and Leon[5] describe subperiosteal new bone deposits occurring in hypervitaminosis A. However, patients seen with infantile cortical hyperostosis have had adequate vitamin intake without excessive vitamin A intake.

Sherman and Hellyer[3] suggest that the primary pathology may involve muscle and vascular tissue on the grounds that these changes, which precede the bony changes, may produce the underlying periosteal reaction.

Tuberculosis, rickets, lues, and scurvy have been adequately ruled out in the cases so far reported. The disease has failed to respond to the administration of vitamins C and D, irradiation, transfusion, and antihistaminic drugs.

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REPORT OF TWELVE CASES OF ACUTE POLIOMYELITIS TREATED WITH BISTRIUM (C 6)*

Special Report No. 223

Stanley Wolf, M.D.
Francis J. Mastrota, M.D.
Joseph M. LoPresti, M.D.

The need for new and more satisfactory drugs to relieve the pain and spasm of acute poliomyelitis prompted the use of Bistrium. This drug is a new ganglionic blocking agent that inhibits transmission through all autonomic ganglia including the sympathetic as well as the parasympathetic. Finnerty and Freis have reported beneficial effects of the drug on peripheral vascular disease and hypertension. They also found the drug to be relatively safe. Having administered it to over one thousand patients, a transient postural hypotension was found to be the most serious side effect. Since this occurs with the first dose, even if it is small, it is thought to be due to individual sensitivity to the drug. Recently the trend has been to treat the muscle spasm of poliomyelitis with vasodilating drugs. This is based on the fact that there is a decreased circulation, as shown by the decrease in skin temperature and the plethysmograph, to areas affected with muscle spasm. Vasodilating drugs such as Priscoline have been used with little beneficial effect. Bistrium was more promising since it has a more potent vasodilating effect than the drugs previously used.

Private and ward patients with severe and moderate muscle spasm were given increasing doses of Bistrium by intramuscular injection. The first dose was ½ milliliter in all cases to determine if the patients were hypersensitive to the drug. Bistrium was then given every 6 hours in doses increasing by ½ to 1 milliliter with each injection until doses of 4 to 5 milliliters were reached.

The patients were evaluated after each injection for changes in blood pressure, subjective feeling, size of pupils, and changes in muscle spasm.

All muscle spasm was graded and recorded. Changes in straight leg raising were recorded in degrees of angulation from the plane of the head. Neck and back spasm was measured from 0 to 4 plus by defined criteria. Each patient was maintained on the drug for at least 5 to 6 days. Hot packs were not applied while the patients received Bistrium.

RESULTS

Eleven patients were treated in the preliminary study. Two of the patients had relief of spasm after five days of treatment. This result is a

* Bistrium, Squibb brand name for hexamethonium.

deviation from the average duration of time to expect spontaneous relief but it is well within the lower time range. This cannot be attributed to be an effect of Bistrium. Nine patients were treated with no beneficial effect. Two of these patients experienced relief from pain when hot packs were applied after Bistrium was discontinued.

All patients experienced mydriasis, but only two complained of blurred vision and dizziness. Two developed obstipation; one other had abdominal distension due to paralytic ileus, and one patient had urinary retention. No patients had any significant drop in the blood pressure. Due to the lack of beneficial results and the increasing incidence of constipation, paralytic ileus, and urinary retention, the drug was not administered to more patients.

SUMMARY AND CONCLUSION

1. Bistrium was given to eleven patients with no significant relief of muscle spasm.
2. Bistrium caused mydriasis, constipation, obstipation, urinary retention.
3. No patients had significant changes in blood pressure.
4. In this small series, Bistrium has failed to relieve muscle spasm of poliomyelitis. The lack of good results discourages its use.

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CLINICO-PATHOLOGICAL CONFERENCE

Directed by: E. Clarence Rice, M.D.
Assisted by: Richard J. Waters, M.D.
By Invitation: Paul C. Kiernan, M.D.
Richard J. Waters, M.D.

This ten year old white male was first seen at Children's Hospital at thirteen months of age for a mild episode of vomiting and diarrhea. These symptoms responded well to a change in diet and a pectin preparation. Physical examination during these visits revealed an essentially normal infant with the exception of marked pallor of the skin and mucous membranes. No abdominal organs were palpable. A hemogram at the first visit disclosed 5 grams of hemoglobin; 2,900,000 erythrocytes; and 8,600 leukocytes of which 40 per cent were granulocytes, 56 per cent lymphocytes, and 4 per cent monocytes. No further evaluation of the hematologic status was attempted. The patient received two transfusions and was discharged to his parents.

During the succeeding nine years his growth and development were normal, however, his mother had noted some tendency towards easy bruising and "lowered resistance," which made him prey to upper respiratory infections. One year of school was repeated because of absences due to these illnesses. His mother noted that he had always been paler than his two siblings, and that he lacked interest in the more vigorous forms of play activity. No episodes of jaundice, hematemesis, or melena were described.

Two months prior to admission he complained of "shooting pains" in the head, chest, abdomen, and knees. These became more severe and two weeks later an episode of fever and non-productive cough was diagnosed as pertussis by his family physician. This illness lasted ten days, and the severe coughing was accompanied by a short episode of epistaxis. Physical examinations by the doctor at this time disclosed an enlarged spleen and following recovery, the patient was sent to Children's Hospital for diagnostic study.

Family history revealed no evidence of heritable, chronic contagious, or hematologic disease.

Physical examination on admission disclosed a well developed but thin white male who appeared moderately listless but in no distress. His temperature was 98.6 F., the pulse was 80 per minute and the respirations, 20 per minute. The mucous membranes and skin were markedly pale. No petechiae were seen but there were several small bruises on the lower extremities. The sclerae were white. The heart was of normal size and no murmurs were heard. The lungs were resonant to percussion and clear to auscultation. The abdomen was protuberant and a venous pattern was noted over the anterior surface. The liver was not palpable, but the spleen was enlarged and extended to the umbilical line inferiorly and to the sternal line anteriorly. It was firm and the edges were rounded. No other abdominal organs were palpable. The anterior cervical, axillary, and inguinal lymph nodes were moderately enlarged and firm. The remainder of the physical examination was essentially negative.

During the first few days following admission, the laboratory studies noted below were performed following which two transfusions of whole blood were given. Examination of the esophagus by means of barium swallow disclosed no abnormality in the mucosal pattern. Two weeks later an operaion was performed.

1. Peripheral Blood	
Hemoglobin	8
Erythrocytes	3,400,000
Leukocytes	1,600
Differential leukocytes count:	
Granulocytes	54%
Neutrophiles	42%
Segmented	11%
Bands	20%
Metamyelocytes	8%
Myelocytes	3%
Basophiles	3%
Segmented	2%
Myelocytes	1%
Eosinophiles	9%
Lymphocytes	46%
Mature	42%
Atypical	4%

Erythrocytes show numerous microcytes and occasional macrocytes with moderate hypochromia, and slight polychromatophilia.
Platelets are slightly reduced. (Rees Ecker) ..... 90,000 per cu. mm.

2. Bone Marrow
Megakaryocytes are present in normal numbers.
L:E 1:1
Differential leukocyte count:

Granulocytes	88%
Neutrophiles	62.5%
Segmented	2.5%
Bands	43.5%
Metamyelocytes	12.5%
Myelocytes	4.0%
Eosinophiles	15.0%
Segmented	4.5%
Bands	7.0%
Metamyelocytes	2.5%
Myelocytes	1.0%
Basophiles	5.5%
Segmented	0.5%
Myelocytes	5.0%
Promyelocytes	5.0%
Lymphocytes	12.0%
Mature	11.5%
Prolymphocytes	0.5%
Erythroid cells (200 counted)	
Megaloblasts	1.0%
Erythroblasts	12.5%
Normoblasts	86.5%

3. Adrenalin Test

Time	*WBC*	*Platelets*	*Pulse*	*B.P.*	*Size of Spleen*
9:30	1500 (diff)	130000	88	120/75	11 cm. below costal margin
9:45	0.5 cc. Adrenalin S.Q.				
10:00	2700	54000	112	190/85	10 cm. below costal margin
10:15	3800 (diff)	66000	112	180/100	9 cm. below costal margin
10:30	3200	56000	116	180/120	7 cm. below costal margin
10:45	2800 (diff)	5800	112	140/85	
11:00	2300	50000	100	130/75	10 cm. below costal margin

4. Urinalysis—Normal.
5. Prothrombin activity—53 per cent.
Prothrombin concentration—87.5 per cent.
6. Thymol turbidity—7.3 units.
7. Total protein: 6.6 gms. per cent.
Albumin—3.98 gms. per cent.
Globulin—2.66 gms. per cent.
A/G—1.5/1
8. Cephalin flocculation 2 plus in 24 hours and 3 plus in 48 hours.
9. Coomb's Test—Negative.

10. Erythrocyte fragility test—Normal fragility.
11. Bromsulfalein Test:
    Spec. #1—No dye.
    30 minute spec.—less than 5%.
    60 minute spec.—no dye.

DISCUSSION

Paul C. Kiernan, M.D.

A discussion of the case presented is a discussion of "hypersplenism" which may be either primary or secondary.

There was some concern relative to liver disease in this individual preoperatively. Hypersplenism then would have existed as a secondary disease, secondary to the liver involvement. It is my impression from the history and findings in this case that there was little to indicate liver disease. The bromosulphalein test was negative and although the thymol turbidity and cephalin flocculation were abnormal, only single tests were done and, in order to diagnose cirrhosis in such an individual, repetition of the tests would have been necessary. There was, in addition, no evidence of portal hypertension; esophageal varices were not visualized on x-ray examination, and there had been no vomiting of blood. There was no evidence of venous collateral circulation as seen on the abdominal wall and on the chest wall. No other stigmata of liver disease were present. Therefore, this discussion will be concerned primarily with that of primary hypersplenism, for the laboratory tests indicate an anemia, a leukopenia, and a thrombocytopenia. There is no report of reticulocyte counts, of an elevated serum bilirubin, or of urobilinogen. Therefore, one would hesitate to say with 100 per cent assurance that this patient has an hemolytic anemia based on hypersplenism, but the impression is that such was present. There certainly is every indication to believe that there was leukopenia based on overactivity of the spleen; in addition, there is evidence to make the diagnosis of thrombocytopenic purpura. The diagnosis in such instances depends upon examination of the peripheral blood with depletion of such, plus examination of the bone marrow showing hyperplasia of these elements.

Much attention is given by many to the use of the adrenalin test in instances of hypersplenism, following the leukocyte count after the injection of ½ milliliter of adrenalin. Others, however, are of the impression that this is of little or no importance in the diagnosis of splenic neutropenia. There seems to be, in this particular instance, response in that there was elevation of the leukocyte count after adrenalin injection. The Coomb's test, reported as negative, as you know, is one to detect the presence of antibodies in the circulating blood, and in instances of hemolytic anemia with a positive Coomb's test there is danger from the use of blood transufsions. In acute hemolytic anemia, with a positive Coomb's test, blood transfusions may

be given only with great caution. However, we now know that such individuals may be treated with adreno-cortico-tropic hormone (ACTH) and be protected against hemolysis which would follow blood transfusion. In individuals with a negative Coomb's test, this precaution is not necessary and they may be transfused preoperatively with safety.

Our knowledge of the spleen has been gained primarily from clinical experience rather than pathologic knowledge of this organ. For many years we have known that individuals with the disease, primary thrombocytopenic purpura, are cured rather dramatically by splenectomy if the diagnosis is accurately made. In addition, we know that individuals with congenital or acquired acute hemolytic anemia, with evidence of hyperplasia of the bone marrow erythroid series are vastly improved or cured by splenectomy.

Rather recently, in 1937, on theoretical grounds, overactivity of the spleen, resulting in a depletion of the circulating leukocytes, was predicated by Wiseman and Doan. It was their impression that such overactivity of the spleen for leukocytes resulted from phagocytic activity of this organ, the phagocytes of the spleen, the reticuloendothelial system, actually engulfing the circulating leukocytes. They drew a similarity between this disease which they termed, "primary splenic neutropenia," to hemolytic anemia in which the spleen was said to phagocytize selectively the circulating red cells of the blood and in primary thrombocytopenic purpura, the phagocytic activity was said by them to be directed against the thrombocytes. It is the impression of others, notably Dameshek, that this activity or overactivity (hypersplenism) is due to an hormonal activity of the spleen, hormones being elaborated by the splenic pulp which interfere with the maturation and delivery of one, several, or all of the formed elements from the bone marrow. Doan, in 1945, defined and differentiated a newly-recognized syndrome, "primary panhematopenia," in which, apparently, in certain individuals, the spleen fails entirely in its pathologic sequestration to discriminate among the formed elements of the blood. There results, by such indiscriminate activity, a peripheral hematologic and clinical picture superficially resembling the hypoplasia in aplastic anemia. Others since that time have reported a number of cases of both primary splenic neutropenia and primary panhematopenia. Just as in individuals correctly diagnosed as primary thrombocytopenic purpura or primary hemolytic anemia with hyperplasia of the bone marorw of these elements; in these diseases, primary splenic neutropenia and primary panhematopenia with hyperplasia of all the elements of the bone marrow, splenectomy is indicated and is rather dramatically curative of the condition.

As we stated originally, hypersplenism may be primary or secondary. Secondary is to be here distinguished from symptomatic. Individuals may

be diagnosed as having symptomatic thrombocytopenic purpura when the depletion of the thrombocytes in the peripheral blood is due to the ingestion of, or overexposure to some drug, but there is here also depletion of the precursors of the thrombocytes in the bone marrow, namely, the megakaryocytes. In secondary hypersplenism when, for instance, the blood platelets are involved (therefore, secondary thrombocytopenic purpura), there is evidence of hyperplasia of the megakaryocytes in the bone marrow. In addition, there is the disease which has caused the increased activity of the spleen. Instances of such are: Hodgkin's disease, lymphosarcoma, chronic leukemia, or other primary tumors of the spleen. In secondary hypersplenism, the spleen is usually enlarged; whereas in instances of primary thrombocytopenic purpura, the spleen is most often small or normal in size. We, therefore, speak of primary thrombocytopenic purpura as "small spleen purpura," whereas, in secondary thrombocytopenic purpura, we speak of such as "large spleen purpura."

The diagnosis in instances of hypersplenism is not difficult so long as one has available excellent hematologic opinion to be rendered relative to the status of both the peripheral blood and the bone marrow, for without accurate examination of the bone marrow great difficulties will be encountered. Patients with symptomatic purpura, with symptomatic hemolytic anemia, or with leukemia, will be inadvertently operated upon for splenectomy when such is definitely to be contraindicated. However, with accurate examination of the peripheral blood, supported by evidence of hyperplasia of one, several, or all of the formed elements of the bone marrow, splenectomy is to be indicated with the hope of good results in the majority of patients. Opinion is erroneously held by many that individuals with acute primary thrombocytopenic purpura, who are bleeding massively, are not candidates for operation and that so-called "conservative regime" should be carried out in order to improve the general condition and thus allow operation to be done at a more minimal risk. The same opinion is held by many for individuals in acute crisis of congenital or acquired hemolytic anemia and later carried out as a "safer procedure." Certainly our experience leads us to believe that this opinion is wrong. Individuals with primary thrombocytopenic purpura of mild degree are not in need of splenectomy in the great majority of instances for such can be followed without danger, but in individuals correctly diagnosed as acute primary thrombocytopenic purpura who are bleeding massively, certainly splenectomy should be carried out without delay, for it is in these instances that it is most dramatically curative. This is the case, also, in hemolytic anemia based on hypersplenism, and if there is evidence of a positive Coomb's test, which was spoken of before, blood transfusions will lead to fatal results in a fair number of patients. Removal of the spleen, therefore, should precede the

giving of blood transfusions. In patients with acquired hemolytic anemia with negative Coomb's test, however, this need not concern one so greatly; for hemolysis, as was previously stated, will not result from blood transfusions.

Very little attention is given to instances of secondary hypersplenism, but we know from rather recent experience that good results may be obtained in individuals with chronic lymphatic leukemia who have hemolytic anemia or thrombocytopenic purpura because of overactivity of an enlarged spleen involved in this chronic disease. Studies of the bone marrow in these cases show hyperplasia of these elements and the removal of the spleen although, of course, having no effect on the primary disease, will relieve the patient of need for multiple blood transfusions or will be of help in controlling blood loss which results from hemorrhage because of a low platelet count. We have had an individual recently with multiple myeloma who had secondary hypersplenism in the form of hemolytic anemia. Before splenectomy he required multiple (three to four) blood transfusions every several days. Following the removal of his spleen he is in need of one pint of blood every five or six weeks. Individuals with portal hypertension with splenomegaly may show evidence of secondary hypersplenism and, in such instances, hemolytic anemia and neutropenia may be improved by splenectomy which may be combined with a shunt procedure of the portocaval type or by anastomosis of the splenic and left renal veins.

Rienhoff has recently advocated a procedure in individuals with portal hypertension due to intrahepatic obstruction resulting from cirrhosis, which if it proves to be successful, will offer a great deal to individuals who suffer from bleeding esophageal varices. This is common hepatic and splenic artery ligation. Splenic artery ligation may, for a time at least, be helpful in controlling the secondary hypersplenism in addition to lowering the portal vein pressure.

Little need be said relative to the technique of splenectomy, for this is a relatively simple operative procedure, however, it was noted in the protocol that splenectomy was carried out through a transthoracic incision. We are all aware of the fact that some procedures, which if accompanied by removal of the spleen, may be more easily carried out through a "combined incision." However, just because there is a great deal more room through which to work and because the spleen is easily delivered, in my judgement, is no justification for the routine transthoracic approach for the removal of the spleen. Advocates of such approach have given the impression that the removal of huge spleens may be carried out only through this type of incision, however, I have recently removed a spleen, fourteen

pounds in weight, by the transabdominal route and it would be my impression, after the removal of such, that it would be delivered only with extreme difficulty through the chest. That, however, is not the point. Simply because the procedure is easier for the operator, by the transthoracic route, in my estimation, is no reason for its routine use in splenectomy. Transabdominally, the operation is withstood very well and complications such as developed in this individual will not be had. Some surgeons advocate preliminary ligation of the splenic artery at the superior border of the pancreas along which this vessel courses. We have not found this to be necessary. In some cases of splenic anemia, because of the many dense vascular adhesions between the spleen and its parietal peritoneal bed, there may be much bleeding when the spleen is elevated into the incision. This can be well controlled by elevation of the spleen, quick packing of the splenic bed, and careful individual ligation of the vessels of the splenic pedicle. Bleeding from the torn adhesions in the parietal peritoneum can be controlled after the spleen has been removed.

The results of splenectomy in the treatment of hypersplenism, if it be primary, are excellent. For secondary hypersplenism the long term results depend, of course, upon the primary disease. However, for the treatment of the hypersplenic factor, the results are fair. The complications of splenectomy are primarily two: (1) The development of thrombophlebitis, either peripheral or phlebitis of the splenic vein. Individuals with thrombocytopenic purpura in whom there is a postoperative high rise of the circulating blood platelets, such rise need not be feared because the development of thrombophlebitis, in these individuals, is a rarity. However, in individuals with other forms of hypersplensim, thrombophlebitis is of more common occurrence than in the average abdominal procedure. (2) In individuals with liver disease, the hepatic involvement has a definite effect on the outcome, for with marked liver disease, as shown by the bromsulphalein test, the survival rate of these individuals is proportionately decreased.

It is my impression, in summary, that the case presented represents a case of primary hypersplenism in which all of the circulating formed elements of the blood are depressed by overactivity of the spleen. Whether such destruction results from phagocytic activity of the spleen itself or by hormonal control of the spleen, exerting its influence on the bone marrow, I am not qualified to state. Laboratory reports of the examination of the blood, however, together with an examination of the bone mrarow indicates that there is destruction of the red cells, hemolytic anemia; destruction of the leukocytes, splenic neutropenia; and destruction of the platelets, thrombocytopenia, all in one individual who is to be, therefore, classified as primary panhematocytopenia.

In closing, I wish to state that I have enjoyed hearing the presentation of this case and wish to thank you for the opportunity of taking part in its discussion.

PATHOLOGIC DISCUSSION

Richard J. Waters, M.D.: We wish to thank Dr. Kiernan for being with us this afternoon and for his most comprehensive discussion of this patient, hypersplenism, and the surgical indications for splenectomy.

Because of the marked pancytopenia, the suggestive adrenalin tests, and the bone marrow smear which indicated marked hyperplasia of the erythroid elements with the eosinophilia, thrombocytopenia, and leukopenia, the diagnosis of hypersplenism was strongly considered by the physicians who attended the patient on the ward. It was the opinion of the pediatrician, a consulting surgeon, and the hematologist that surgical removal of the spleen offered the best possibility for the complete cure of the patient. Following adequate preparation and transfusions of whole blood, a splenectomy was performed through a transthoracic approach. During the procedure an attempt was made to cannulate one of the larger stems of the portal system, and water manometer readings indicated a moderate increase in the normal expected pressure. The spleen weighed four times normal for the age group. The capsule was mottled dark red and purple and was wrinkled. The organ cut with increased resistance and the cut surface was homogeneous, red, and smooth. No malpighian bodies were seen. Smears of the splenic pulp were made and stained with Wright's stain. These disclosed large numbers of thrombocytes. Evidence of moderate thrombocytophagocytosis, but no evidence of erythrophagocytosis or leukophagocytosis was found. Microscopic section of the spleen revealed marked increase in the reticular connective tissue of the spleen, engorgement of the sinusoids, some increase in the reticuloendothelial elements, and compression of the malpighian bodies. The histologic picture was compatible with the diagnosis of congestive splenomegaly. A section of liver tissue, removed by biopsy during the splenectomy, disclosed essentially normal hepatic architecture.

Postoperative hemograms are noted in Chart 1.

Operation	9.5 grams	4,000,000	1,700	30,000
1st post op.	13.0 grams	5,200,000	34,900	34,000
2nd post op.	12.0 grams	3,700,000	9,200	134,000
3rd post op.	11.8 grams	4,400,000	9,200	700,000
4th post op.	12.0 grams	3,900,000	12,900	515,000
5th post op.	13.5 grams	4,600,000	18,000	369,000
6th post op.	12.0 grams	4,200,000	6,600	314,000
7th post op.	14.0 grams	3,900,000	9,300	280,000

The patient received approximately 450 milliliters of whole blood during and after the operation. There was a marked response from the whole blood noted on the first day after operation. The postoperative course was complicated by pneumothorax on the left with marked collapse of the left lung. This responded, however, in a few days to constant closed drainage. As seen in Chart 1, there was a marked and lasting response in hemoglobin, erythrocyte level and thrombocyte level. It can be seen that on the third postoperative day, the thrombocytes were 700,000 and this might be explained by moderate dehydration which accompanied the toxicity in association with the atelectasis. Platelet counts were normal during the remainder of the hospital stay and have remained at normal levels since. Thymol turbidity and cephalin flocculation tests which preoperatively were somewhat abnormal had returned to normal range four weeks after operation. The patient is active, happy, and the follow-up hemogram level revealed normal values for hemoglobin, erythrocytes, and thrombocytes.

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